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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 237/32

A1

(11) International Publication Number: WO 97/22594

(43) International Publication Date: 26 June 1997 (26.06.97)

(21) International Application Number: PCT/DK96/00534

(22) International Filing Date: 16 December 1996 (16.12.96)

(30) Priority Data:
1419/95 15 December 1995 (15.12.95) DK

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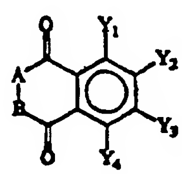
(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: COMBINATORIAL LIBRARIES



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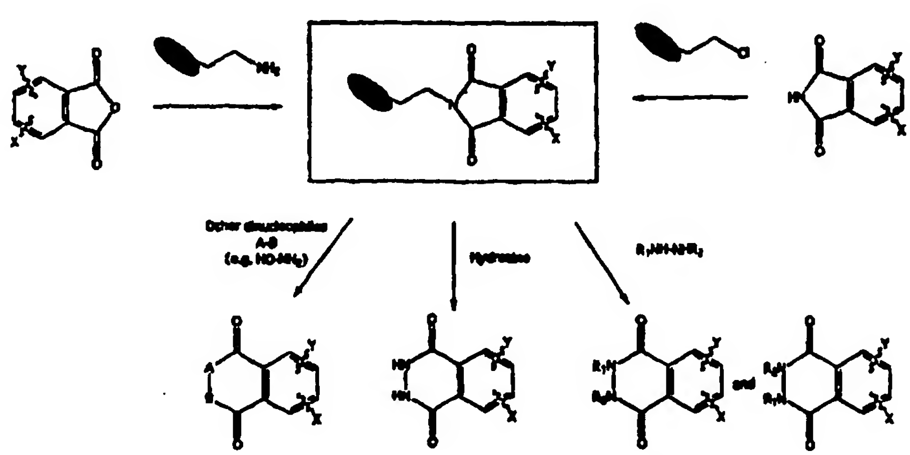

(57) Abstract

The invention provides a method for the production of a combinatorial library of compound of general formula (I) using solid phase methodologies. The cleavage of the array of immobilised compounds of the phthalimido type from the solid support matrix is accomplished by using an array of dinucleophiles, e.g. hydrazines (hydrazinolysis) or N-hydroxylamines, whereby a combinatorial dimension is introduced in the cleavage step. The invention also provides a compound library.

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FIELD OF THE INVENTION

COMBINATORIAL LIBRARIES

The present invention relates to a method for producing a combinatorial library of compounds of the general formula I defined herein. The method involves the use of a support material on which an array of intermediates is covalently attached. Such intermediates may undergo reactions before cleavage for the support units. In the cleavage step, an array of different reagent species may be used, thereby introducing a combinatorial dimension in the cleavage step. The present invention also relates to a library of two or more compound of the general formula I.

BACKGROUND OF THE INVENTION

In traditional medicinal chemistry, an average of 10,000 different compounds are synthesised and tested during the process of finding the one active component with the right pharmacological and toxicological properties (the drug). The combined experiences from a series of analytical, crystallographic, synthetic organic and computational chemistry techniques have been collected and generated a whole new field often termed "Rational Drug Design". These methods have been expected to speed up and facilitate the search for new lead compounds and drugs, but have so far not proven very effective. Today the average cost for a new drug still runs around US$ 250-350,000,000 and it takes an average of 12 years for a new drug to reach the market place. Furthermore, in spite of obvious scientific progress during the last couple of decades, many diseases are still threatening mankind because of no or insufficient treatment. These obviously include AIDS, cardiovascular diseases and human cancers but also diseases related to neuro-degenerative disorders (e.g. Alzheimer's disease), metabolic disorders (Type 2 Diabetes) and other diseases affecting not only the quantity but also the quality of life.

To facilitate this search for novel biologically active compounds, a new chemical/analytical technique has emerged. This research area is often termed combinatorial chemistry and it is one of the fastest growing research areas in modern organic chemistry. The synthesis and screening of vast and diverse libraries of small molecules might lead not only to new drugs but might also have a great importance for the discovery of novel synthetic receptors, new materials or new catalysts. Most of the reported literature in this field have been concerned with libraries consisting of small peptides and oligonucleotides because synthetic protocols for solid-phase synthesis of these molecules have been optimised for decades. However, small molecules represent a larger challenge for the synthetic organic chemist as well hold the potential for finding possible leads for the drug discovery process.

The generation of chemical diversity using combinatorial chemistry is one of the most active fields of modern organic chemistry. Initially, research was focused on the generation on peptide

and nucleotide libraries but more recently - due to the dubious drug-potential of these compounds - the generation of non-peptidic small molecule libraries have attracted most of the attention and resources in this field.[1-3]

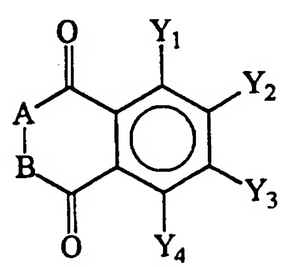
Recently, some reports on the generation of small molecule libraries in solution appeared,[4-5] but still, the majority of the published work in the area of generating combinatorial small molecule libraries are performed using solid-phase chemistry. The original reason for this was the fact that using a solid-phase approach, the split-mix-recombine method[6-7] could be used as a way of generating truly vast libraries. Now, when many people are focusing on fewer (or even single compounds) per vial ("sub-library"), the solid-phase methods have retained its popularity - most probably due to its ease of automation of solid-phase chemistry as compared to standard solution organic synthesis.

Therefore, combinatorial libraries are generally synthesised using solid-phase synthesis which leave the individual members with one specific functional group in common (typically a phenol, a carboxylic acid, an amide, etc.) after deprotection and cleavage from the solid support.[8] Thus, this functionality is required for linking the group of molecules covalently to the solid-support during the course of synthesis.

SUMMARY OF THE INVENTION

The present invention relates to a method for producing a combinatorial library of chemical compound following solid phase methodology, where a combinatorial dimension can, and often will, be introduced in the step where the chemical entities are liberated from the support material.

Thus, the present invention provides a method for producing a combinatorial library of compounds of the general formula



I

wherein each of A and B independently is selected from the group consisting of -N(R^1)-, -O-, -S-, -Se-, and -Te-,

wherein each R^1 independently designates hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally

substituted C_{6-20}-alkatrienyl, optionally substituted C_{2-20}-alkynyl, optionally substituted aryl, optionally substituted heteroaryl, and

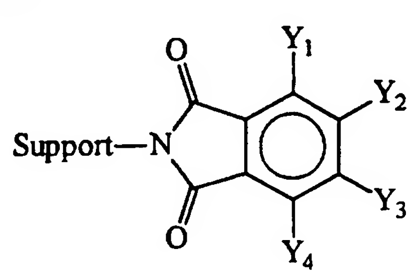
each of Y_1, Y_2, Y_3, and Y_4 independently designates hydrogen; optionally substituted C_{1-20}-alkyl; optionally substituted C_{2-20}-alkenyl; optionally substituted C_{4-20}-alkadienyl; optionally substituted C_{6-20}-alkatrienyl; optionally substituted C_{2-20}-alkynyl; hydroxy; optionally substituted aryl; optionally substituted aryl-C_{1-6}-alkyl; optionally substituted aryloxy-C_{1-6}-alkyl; optionally substituted heteroaryl; optionally substituted heteroaryl-C_{1-6}-alkyl; optionally substituted heteroaryloxy-C_{1-6}-alkyl; halogen such as fluoro, chloro, bromo, and iodo; cyano; nitro; O-R^2; formyl, carboxy, -CO-O-R^2, -CO-R^2, -O-CO-R^2; amino; -N(R^2)H; mono- or di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl; -N(R^2)R^3; -N(R^3)-CO-R^2; (C_{1-20}-alkyl)carbonylamino-C_{1-6}-alkyl; carbamoyl, aminocarbonyl-C_{1-6}-alkyl; mono- or di-(C_{1-20}-alkyl)aminocarbonyl; mono- or di(C_{1-6}-alkyl)aminocarbonyl-C_{1-6}-alkyl; sulphanyl; optionally substituted C_{1-20}-alkylthio-C_{1-6}-alkyl; optionally substituted alkylthio; (optionally substituted aryl)thio; guanidino; guanidino-C_{1-6}-alkyl; sulphono (-SO_3H); sulphino (-SO_2H); halosulphonyl; -$S(O)_m$-$N(R^2)_2$ where m is 2 or 3; -$S(O)_m$-NH(R^2) where m is 2 or 3; -$S(O)_m$-NH_2 where m is 2 or 3; isocyano; isothiocyano; thiocyano; -$OP(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; and -$N(R^3)P(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5;

wherein each R^2 independently designates a group selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted C_{2-20}-alkynyl, optionally substituted aryl, optionally substituted heteroaryl; and R^3 independently designates a group selected from hydrogen and C_{1-6}-alkyl;

or one or two of the substituent pairs, Y_1/Y_2, Y_2/Y_3, Y_3/Y_4, may each form a biradical which, together with the atoms located between the substituents in question, form(s) either a 4-, 5-, 6-, 7- or 8-membered ring, where the biradical is a 2-, 3-, 4-, 5-, or 6-membered partially or fully saturated carbon chain optionally interrupted and/or terminated by one or more heteroatoms selected from nitrogen, oxygen, and sulphur, and where the biradical may be substituted with one, two, three, or several substituents as defined for Y^1-Y^4;

comprising

(a) providing an array {P} of at least two different support-immobilised phthalimido moiety species of the general formula II



II

wherein "Support" indicates a polymeric support unit to which the phthalimido moiety species are covalently bound, and Y_1, Y_2, Y_3, and Y_4 are as defined above,

and (b) cleaving the support-immobilised phthalimido moiety species, or a least a part thereof, from the support units to which they are immobilised by reacting the support units with an array {D} of at least one, preferably at least two, dinucleophile species of the general formula A'-B' (corresponding to A-B in formula I), wherein each of A' and B' independently is selected from the group consisting of -N(R^1)H, -OH, -SH, -SeH, -TeH, wherein each R^1 is as defined above; whereby the 5-membered ring of the phthalimido moiety (formula II) is converted to a 6-membered ring (formula I), the identity of which is dependent of the identity of the dinucleophile (A'-B') with which the moiety species has been reacted.

Thus, the method give rise to a series of new structurally diverse compounds. Furthermore, the linking, deprotection and cleavage schemes are potentially very useful for the generation of different attractive combinatorial library formats.

DETAILED DESCRIPTION OF THE INVENTION

In the present context, the term "C_{1-20}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 20 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, cyclopropyl, butyl, *tert*-butyl, iso-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl, hexadecyl, heptadecyl, octadecyl, nonadecyl. Analogously, the term "C_{1-6}-alkyl" is intended to mean a linear, cyclic or branched hydrocarbon group having 1 to 6 carbon atoms, such as methyl, ethyl, propyl, iso-propyl, cyclopropyl, butyl, *iso*-butyl, *tert*-butyl, cyclobutyl, pentyl, cyclopentyl, hexyl, cyclohexyl.

Preferred examples of "alkyl" are methyl, ethyl, propyl, iso-propyl, butyl, *tert*-butyl, iso-butyl, pentyl, cyclopentyl, hexyl, cyclohexyl, in particular methyl, ethyl, propyl, iso-propyl, *tert*-butyl, iso-butyl and cyclohexyl.

Similarly, the terms "C_{2-20}-alkenyl", "C_{4-20}-alkadienyl", and "C_{6-20}-alkatrienyl" are intended to mean a linear, cyclic or branched hydrocarbon group having 2 to 20, 4 to 20, and 6 to 20, carbon atoms, respectively, and comprising one, two, and three unsaturated bonds, respectively. Examples of alkenyl groups are vinyl, allyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, heptadecaenyl. Examples of alkadienyl groups are butadienyl, pentadienyl, hexadienyl, heptadienyl, heptadecadienyl. Examples of alkatrienyl groups are hexatrienyl, heptatrienyl, octatrienyl, and heptadecatrienyl. Preferred examples of alkenyl are vinyl, allyl, butenyl, especially allyl.

Similarly, the term "C_{2-20}-alkynyl" is intended to mean a linear or branched hydrocarbon group having 2 to 20 carbon atoms and comprising a triple bond. Examples hereof are ethynyl, propynyl, butynyl, octynyl, and dodecaynyl.

In the present context, i.e. in connection with the terms "alkyl", "alkenyl", "alkadienyl", "alkatrienyl", and "alkynyl" the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-3 times, with group(s) selected from hydroxy, C_{1-6}-alkoxy (i.e. alkyl-oxy), carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkanoyloxy, sulphono, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, C_{1-6}-alkylthio, trihalogenalkyl, halogen such as fluoro, chloro, bromo or iodo, where aryl and heteroaryl may be substituted with methyl, methoxy, nitro or halogen.

Preferably, the substituents are selected from hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C_{1-6}-alkyl)amino, carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, trihalogenalkyl, halogen such as fluoro, chloro, bromo or iodo, where aryl and heteroaryl may be substituted with methyl, nitro or halogen. Especially preferred examples are hydroxy, C_{1-6}-alkoxy, carboxy, aryl, heteroaryl, amino, sulfanyl, mono- and di(C_{1-6}-alkyl)amino, mono- and di(C_{1-6}-alkyl)amino, and halogen such as fluoro, chloro, bromo or iodo.

In the present context the term "aryl" is intended to mean an aromatic carbocyclic ring or ring system, such as phenyl, naphthyl, anthracyl, phenanthracyl, pyrenyl, benzopyrenyl, fluorenyl and xanthenyl, among which phenyl is a preferred example.

The term "heteroaryl" is intended to mean an aryl group where one or more of the carbon atoms have been replaced with heteroatoms, e.g. nitrogen, sulphur, and/or oxygen atoms. Examples of such heteroaryl groups are oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrrolyl, imidazolyl, pyrazolyl, pyridinyl, pyrazinyl, pyridazinyl, piperidinyl, coumaryl, furyl, quinolyl, indolyl, benzopyrazolyl, phenoxazonyl. Preferred heteroaryl groups are pyridinyl, benzopyrazolyl, and imidazolyl.

In the present context, i.e. in connection with the terms "aryl" and "heteroaryl", the term "optionally substituted" is intended to mean that the group in question may be substituted one or several times, preferably 1-5 times, with group(s) selected from hydroxy (which when present in

an enol system may be represented in the tautomeric keto form), C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, formyl, aryl, aryloxycarbonyl, arylcarbonyl, heteroaryl, amino, mono- and di(C_{1-6}-alkyl)amino; carbamoyl, mono- and di(C_{1-6}-alkyl)aminocarbonyl, amino-C_{1-6}-alkyl-aminocarbonyl, mono- and di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl-aminocarbonyl, C_{1-6}-alkylcarbonylamino, guanidino, carbamido, C_{1-6}-alkanoyloxy, sulphono, C_{1-6}-alkylsulphonyloxy, nitro, sulphanyl, trihalogenalkyl, halogen such as fluoro, chloro, bromo or iodo. Preferred examples are hydroxy, C_{1-6}-alkoxy, carboxy, C_{1-6}-alkoxycarbonyl, C_{1-6}-alkylcarbonyl, aryl, amino, mono- and di(C_{1-6}-alkyl)amino, aryl and halogen such as fluoro, chloro, bromo or iodo.

In a preferred embodiment of the present invention each of Y_1, Y_2, Y_3, and Y_4 independently designates hydrogen; optionally substituted C_{1-6}-alkyl; hydroxy, optionally substituted aryl; optionally substituted aryl-C_{1-6}-alkyl; optionally substituted aryloxy-C_{1-6}-alkyl; optionally substituted heteroaryl; optionally substituted heteroaryl-C_{1-6}-alkyl; optionally substituted heteroaryloxy-C_{1-6}-alkyl; halogen; cyano; nitro; O-R^2; formyl, carboxy, -CO-O-R^2, -CO-R^2, -O-CO-R^2; amino; -N(R^2)H; mono- or di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl; -N(R^2)R^3; -N(R^3)-CO-R^2; (C_{1-20}-alkyl)carbonylamino-C_{1-6}-alkyl; carbamoyl, aminocarbonyl-C_{1-6}-alkyl; mono- or di-(C_{1-6}-alkyl)aminocarbonyl; mono- or di(C_{1-6}-alkyl)aminocarbonyl-C_{1-6}-alkyl; sulphanyl; sulphono (-SO_3H); sulphino (-SO_2H); halosulphonyl; -$S(O)_m$-N$(R^2)_2$ where m is 2 or 3; -$S(O)_m$-NH(R^2) where m is 2 or 3, -$S(O)_m$-NH_2 where m is 2 or 3; isocyano; isothiocyano; thiocyano; -OP$(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; and -N(R^3)P$(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5;

wherein each R^2 independently designates a group selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted aryl, optionally substituted heteroaryl; and R^3 independently designates a group selected from hydrogen and C_{1-6}-alkyl;

or one or two of the substituent pairs, Y_1/Y_2, Y_2/Y_3, Y_3/Y_4, may each form a biradical which, together with the atoms located between the substituents in question, form(s) either a 4-, 5-, 6-, 7- or 8-membered ring, where the biradical is a 2-, 3-, 4-, 5-, or 6-membered partially or fully saturated carbon chain optionally interrupted and/or terminated by one or more heteroatoms selected from with from nitrogen, oxygen, and sulphur, and where the biradical may be substituted with one, two, three, or several substituents as defined for Y^1-Y^4.

In an especially preferred embodiment of the present invention, each of Y_1, Y_2, Y_3, and Y_4 independently designates hydrogen; optionally substituted C_{1-6}-alkyl; hydroxy, optionally substituted aryl; optionally substituted aryl-C_{1-6}-alkyl; optionally substituted aryloxy-C_{1-6}-alkyl; optionally substituted heteroaryl; optionally substituted heteroaryl-C_{1-6}-alkyl; optionally substituted heteroaryloxy-C_{1-6}-alkyl; halogen; cyano; nitro; O-R^2; formyl, carboxy, -CO-O-R^2, -CO-R^2, -O-CO-R^2; amino; -N(R^2)H; mono- or di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl -N(R^2)R^3; -N(R^3)-CO-R^2;

(C_{1-20}-alkyl)carbonylamino-C_{1-6}-alkyl; carbamoyl, aminocarbonyl-C_{1-6}-alkyl; mono- or di-(C_{1-20}-alkyl)aminocarbonyl; mono- or di(C_{1-6}-alkyl)aminocarbonyl-C_{1-6}-alkyl; sulphanyl; sulphono (-SO_3H); sulphino (-SO_2H);

wherein each R^2 independently designates a group selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted heteroaryl; and R^3 independently designates a group selected from hydrogen and C_{1-6}-alkyl.

In an alternative embodiment, one of the substituent pairs, Y_1/Y_2, Y_2/Y_3, Y_3/Y_4, may each form a biradical which, together with the atoms located between the substituents in question, form(s) either a 4-, 5-, 6-, 7- or 8-membered ring, where the biradical is a 2-, 3-, 4-, 5-, or 6-membered partially or fully saturated carbon chain optionally interrupted and/or terminated by one or more heteroatoms selected from with from nitrogen, oxygen, and sulphur, and where the biradical may be substituted with one, two, three, or several substituents as defined for Y^1-Y^4.

It is envisaged that when any of the substituent pairs Y_1/Y_2, Y_2/Y_3, and Y_3/Y_4 form(s) a biradical, this biradical, together with the atoms located between the substituents in question, represents a ring fused to the bicyclic ring system represented by the formula I, the ring being selected from benzene, furane, 2,3-dihydrofuran, 2,5-dihydrofuran, isoxazole, oxazole, thiazole, isothiazole, imidazole, triazole, cyclobutene, pyroline, pyrrole, cyclopentene, cyclopentadiene, cyclohexene, and cyclohexadiene. These fused rings may in themselves be substituted by one or more substituents as defined for Y^1-Y^4.

As it will be evident from the definition of possible substitutent in formula I, there may be one or more asymmetric carbon atoms present in the molecule depending on the nature of the substituents. The compounds of the invention are intended to include all stereoisomers arising from the presence of any and all isomers as well as mixtures thereof, including racemic mixtures. Also, the compounds may be in the form of alkali metal salts or acid addition salts.

With respect to the dinucleophile A'-B' corresponding to A-B in the general formula I, it should be understood that N-substituted hydrazines, N-hydroxylamines and the S, Se, and Te analogues of N-hydroxylamines are especially relevant. Thus in the general formula I, one of A and B is preferably -N(R^1)- and the other is selected from the group consisting of -N(R^1)-, -O-, -S-, -Se-, and -Te-, preferably -N(R^1)- and -O-, in particular -N(R^1)-, wherein each R^1 independently designates hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted C_{2-20}-alkynyl, optionally substituted aryl, optionally substituted heteroaryl. Preferably R^1 designates hydrogen, C_{1-6}-alkyl, optionally substituted aryl, optionally substituted heteroaryl. It should be understood that the dinucleophile A'-B' corresponds to A-B in formula I.

In the cases where the phthalimido group is asymmetrical, and where the dinucleophile is not a symmetrically substituted hydrazine, it is envisaged that the cleavage reaction will result in two different compounds of the general formula I. Thus, in this way a further diversity of the combinatorial library can be introduced. The reaction between the dinucleophile and the support-immobilised phthalimido moiety is illustrated in Figure 1.

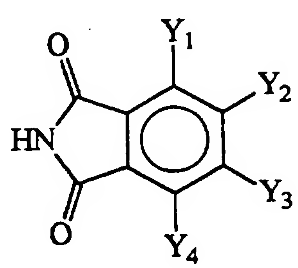
In the trivial case, the array of dinucleophiles consists of only one type of dinucleophile. However it is preferred (in order to fully exploit the principles of the present invention) that the array {D} of dinucleophiles consists of at least two, preferably three, such as four, different dinucleophile species. In a special variant, 2-6 different dinucleophiles constitute the array {D}.

The array {P} preferably consists of at least three, preferably four, such as five, different support-immobilised phthalimido moiety species. In a special variant of the present invention, the array {P} is constituted by 4-15 different phthalimido moieties of the general formula II.

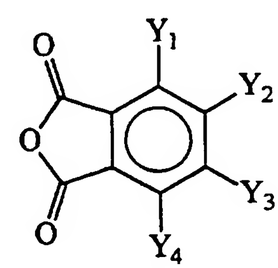
Thus, the present invention provides a method for producing a combinatorial library {D}={P} comprises at least 10, such as from 10 to 100, different species of the formula I.

In the present context, the term "support unit" is intended to mean the individual physical particles of a support material. Such support units may be provided as spheres, sheets, pellets, etc.

The array {P} of support-immobilised phthalimido moiety species of the general formula II may be provided by immobilising an array $\{P_{ab}\}$ of phthalimido moieties of the general formula IIa or IIb



IIa



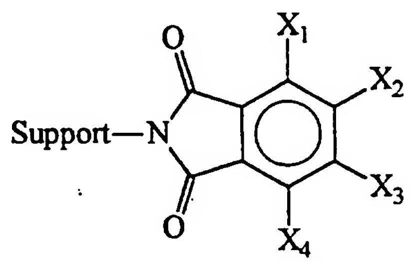
IIb

wherein Y_1, Y_2, Y_3, and Y_4 designate the same groups as defined for the support-immobilised phthalimido moieties of the formula II constituting the array {P} of support-immobilised phthalimido moieties of the general formula II, to a solid support material. As is illustrated in Figure 1, the immobilisation of IIa and IIb requires that the support material comprises an alkyl halide group or an amino alkyl group, respectively. In the case of IIa, an alkali metal salt, e.g. the sodium or potassium salt, may be used.

It is envisaged that any of number of readily available, e.g. commercially available, support material may be used, and that the immobilisation of the compound of the general formula IIa may be attached the support material following method generally known to the person skilled in the art. The methods for immobilising a compound to a support material are well-described for peptides, but also apply for the compounds of the general formula IIa and IIb, see e.g. the well-established Merrifield solid phase synthesis methodology,[14] method derived thereof, and the general methodologies described in references 1-7.

As described above and illustrated in the following, a compound library {D}={P} of compounds of the formula I may be performed simply by attaching an array $\{P_{ab}\}$ of compound of the general formula IIa and/or IIb to a support material followed by cleavage of the immobilised moieties of the formula II from the solid support material. However, in order to exploit the full scope of the present invention, one or more reactions may be performed on the support-immobilised moieties before cleavage.

Thus, in an interesting embodiment of the present invention, the method comprises attaching phthalimido moieties to units of a support to obtain an array {P} of support-immobilised phthalimido moiety species of the general formula III



III

in which "Support" indicates a polymeric support to which the phthalimido moieties are covalently bound, and each of X_1, X_2, X_3, and X_4 independently designate substituents or biradicals as defined for Y_1, Y_2, Y_3, and Y_4; and

performing one or several chemical reactions by contacting the support units carrying the immobilised phthalimido moieties, either together or divided into subgroups of units, with one or several reagents, the contacting in the case of several reagents being performed simultaneously or sequentially, or by using combinations of simultaneous contacting and sequential contacting; whereby an array of support-immobilised phthalimido moiety species of the general formula II is provided. Any necessary protection and deprotection steps should be considered included by the term "one or several chemical reactions".

It is clear that when performing a number of reaction steps, which may be performed on a subgroup of support units only, offers the possibility of introducing further combinatorial dimensions in the combinatorial libraries. The individual reactions performed will be the

reactions normally performed for, or especially adapted to, support-immobilised compounds, of course with due consideration to the support material used.

The present invention furthermore provides a composition comprising at least two different compounds of the general formula I defined above. The composition preferably comprises at least four, preferably at least six, in particular at least ten, such as between 10 and 100, different compounds of the general formula I. The composition is preferably obtained by the method according to the present invention, however, compound libraries which are produced by methods which differs from this method, but which result in a similar combinatorial library should also be considered as falling within the present invention.

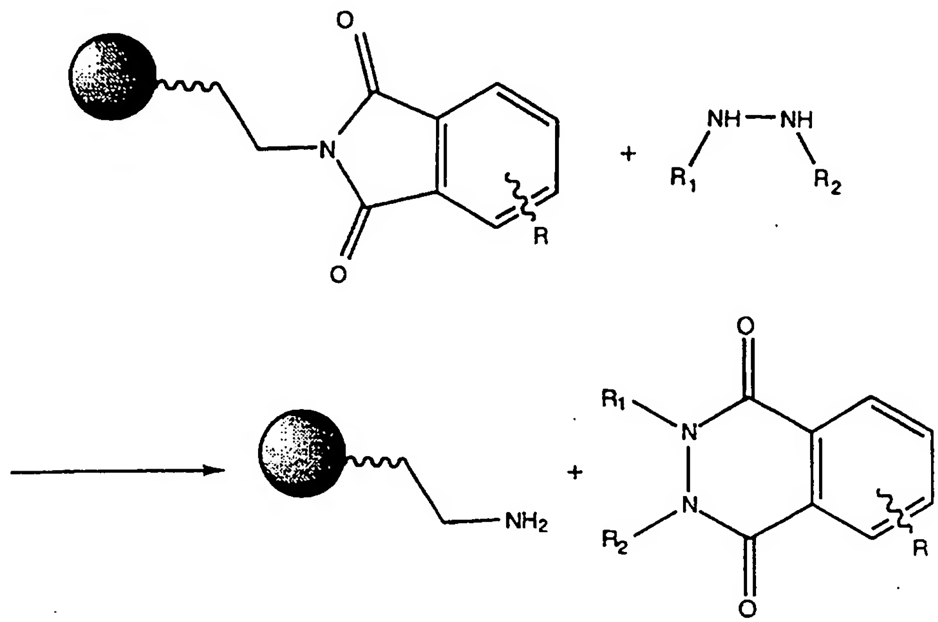
Such as composition, which typically is the crude product of the cleavage reaction, optionally obtained after a simple chromatographic process, e.g. filtering through silica gel, may, if desirable for the reason of solubility, may comprise the compounds of the formula I in the form of salts or acid addition salts thereof. It is naturally desirable that the compound are soluble in the solvent chosen. The solvent used for the composition may be any solvent suitable for screening purposes, such as water, ethanol, methanol, dimethylsulphoxide (DMSO), DMF, and mixtures thereof, etc. The solvent need not necessarily be the same as for the reactions performed on the immobilised moieties or for the cleavage reaction. For screening purposes, it may be essential that the composition according to the present invention, except for any solvents, is substantially free of compounds not being of the formula I, so that any positive response unambiguously can be related to a compound comprised in the composition.

Discussion of the illustrative experiments

The present invention is illustrated in the following, where the dinucleophile is illustrated by various hydrazides. A more specific description of the experiments can be found in the experimental section.

The applicants have for some time been interested in new strategies for the generation of molecular diversity. These include the introduction of a combinatorial cleavage and deprotection scheme i.e. a strategy where a number of different compounds are created during the cleavage and/or deprotection step from the solid-support.[9] Using this strategy, multiple functionalities can be generated systematically such that large numbers of structurally diverse compounds can be created from one common synthon (see Figure 1). In this approach, the small organic moiety is linked to the solid phase through a phthalimide function. The phthalimide function is a fairly stable linkage which still allows for selective cleavage by hydrazines under mild conditions - a reaction known as the Ing-Manske procedure.[10] (Scheme 1). The products of these reactions are phthalhydrazides (2,3-dihydro-phthalazine-1,4-diones) which are known to posses a wide range

of different biological activities and at the same time phthalhydrazides comprise a rather unexplored group of potentially new drug leads.[11,12]

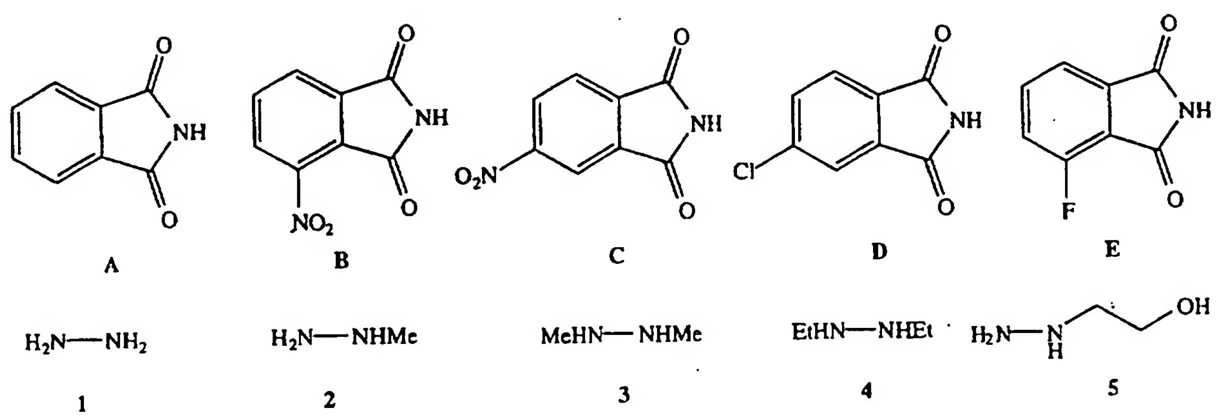


Scheme 1. The Ing-Manske procedure for cleavage of the phthalimide linkage by a hydrazine.

As a model study for the above combinatorial cleavage and deprotection scheme, a systematic study of the reaction between a series of hydrazines (the dinucleophile) and phthalimide has been performed. In these experiments, a number of di-aromatic, mono-aromatic and aliphatic hydrazines were investigated as well as a series of different reaction conditions such as variation of solvent, temperature and the addition of a series of possible catalysts. These reaction optimisations were all carried out in a fashion we have termed "experimental design" using a 2D-matrix having e.g. the solvents in one dimension and the different catalysts in the other dimension. An illustrative example employing 2-hydroxyethylhydrazine as the dinucleophile, 4 different solvents (MeOH, EtOH, N,N-dimethylformamide (DMF) and HOAc) and 6 different catalytic conditions (none, N,N-diisopropylethylamine (DIPEA) (1 and 2 eq.), 4-dimethylamino-pyridine (DMAP) (0.1 and 1 eq.) and trifluoroacetic acid (TFA)) is shown in Scheme 2. From this and the other reaction schemes (which are not included) it was found that excellent reaction conditions were reactions at room temperature, methanol (or ethanol) as the solvent and catalysing the reaction with 2-3 eq. of N,N-diisopropylethylamine (Some hydrazines are available only as the mono- or dihydrochloride, for which reason 3 eq. of catalyst (N,N-diisopropylethyl-amine) is preferable). It was also found that aliphatic hydrazides were more likely to lead to a complete and smooth conversion of the phthalimide into the corresponding end product.

Scheme 2 (see Figure 3) shows an experimental design optimisation of solution reaction between phthalimide and 2-hydroxyethylhydrazine (2 hours reaction time, room temperature, determined by RP-HPLC). HOAc*: For acetic acid, the catalysts were different (1 eq. NaOAc, 2 eq. NaOAc, 1 eq. TFA, 2 eq. TFA and H_2SO_4 [catalytic amount, 2 drops/1 mmole], respectively).

In order to expand the scope of this reaction, 5 different hydrazines were set up to react with 5 different phthalimides in a 6 x 6 matrix format yielding 25 individual compounds (plus 8 isomers), 10 indexed sublibraries[6a] and 1 full library containing a mixture of all 33 different compounds (Scheme 3). The reactions were carried out in the 1 mmole scale and in all cases with the 25 individual compounds we obtained a high yield of the expected phthalhydrazides including 8 isomers (from B2-E2 and B5-E5). Likewise, using reversed-phase HPLC (RP-HPLC), we were able to resolve all individual compounds in the indexed libraries whereas the full 33-member library did not allow resolution and identification of individual compounds.



Scheme 3a. The 5 different phthalimides (A-E) and 5 different hydrazines (1-5) tested in the 6 x 6 matrix solution experiment.

	A	B	C	D	E	
1	A1	B1	C1	D1	E1	[A-E]1
2	A2	B2	C2	D2	E2	[A-E]2
3	A3	B3	C3	D3	E3	[A-E]3
4	A4	B4	C4	D4	E4	[A-E]4
5	A5	B5	C5	D5	E5	[A-E]5
	A[1-5]	B[1-5]	C[1-5]	D[1-5]	E[1-5]	[A-E][1-5]

Scheme 3b. The schematic format of the 6 x 6 matrix (IKA-Vibrax-VXR shaker equipped with an Janke & Kunkel VX2 rack)

Finally, to test this approach on solid-phase, phthalimides A and C were immobilised to a chloromethylated polystyrene resin (Merrifield resin) using a known procedure.[13] The resulting resins contained the expected substituted phthalimide structures according to IR spectroscopy. However, deprotection of phthalimides A and C using hydrazine 5 in EtOH at room temperature was sluggish whereas the expected products A5 and C5 were obtained after reflux for 16 h. When the deprotection was performed in dichloromethane at room temperature, the expected products were obtained in high yields under mild conditions. Likewise, when the resin containing C was reacted with hydrazine 1 in 1,2-dichloroethane (DCE) led to C1 in nearly quantitative yield. Reactions performed in N,N-dimethylformamide did not provide us with any product in the cases tested, indicating a sluggish reaction in dipolar, aprotic solvents just as in the solution experiments, although the resin is well solvated.

The synthetic scheme for the generation of diverse libraries of phthalhydrazides both by solid-phase synthesis, by solution synthesis and in several different combinatorial formats (single compounds, indexed libraries and full libraries) has proved useful. Likewise, using this synthetic scheme as a combinatorial deprotection method combined with solid-phase synthesis of structures linked via a phthalimide linkage, yields another diversity introducing step in a hitherto unknown fashion. The reactions are solvent dependent and during the solid-phase synthesis depend furthermore on the swelling and solvatisation of the resin. The synthetic schemes for the solid-phase reactions to include more complicated structures, optionally involving one or more chemical reactions before cleavage, can be established for the person skilled in the art by using method generally described for solid phase chemistry.

The study of several strategies for generating combinatorial libraries of new small organic molecules (MW < 700 D) has resulted in the present invention. The invention may includes the introduction of a combinatorial cleavage and deprotection scheme. Combinatorial libraries are generally synthesised using solid-phase synthesis and because of this most small molecule libraries leave the individual members with one specific functional group (typically a phenol, a carboxylic acid, an amide, etc.) after deprotection and cleavage from the solid support. According to the strategy of the present invention, multiple functionalities are generated systematically such that large numbers of structurally diverse compounds can be created from one common synthon.

Because of the inherited stability of the phthalimide linkage, this linkage allows a wide range of chemistries to be performed as exemplified in Scheme 3. Functionalised phthalimide derivatives are coupled to amino acids (e.g. the 20 naturally encoded amino acids and a range of unnatural amino acids. β-Amino acids could be used as well and would thus form a product having a 7-membered ring). The resulting acid function can then either be reduced to the corresponding alcohol function and may be further converted to the corresponding alkyl halide or converted directly to the corresponding acyl halide. These alkyl and acyl halide are the ring closed by the Friedel-Craft procedure (see Figure 2).

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EXPERIMENTAL

Synthesis of 4-nitrophthalhydrazide

4-nitrophthalimide (221 mg) was suspended in ethanol (5 ml) and hydrazine (73 µl, approx. 74 mg) was added and the reaction mixture was shaken over night at 1000 rpm. HPLC analysis of reaction mixture showed complete conversion of starting material to 4-nitrophthalhydrazide product (UV_{max} = 248 nm).

Synthesis of N-methyl-4-nitrophthalhydrazide

4-nitrophthalimide (229 mg) was suspended in ethanol (5 ml) and methylhydrazine (73 µl, approx. 74 mg) was added and the reaction mixture was shaken over night at 1000 rpm. HPLC analysis of reaction mixture showed complete conversion of starting material to two isomers of N-methyl-4-nitrophthalhydrazide product (UV_{max} = 248 nm).

Synthesis of N-(2-hydroxyethyl)-phthalhydrazide

2-Hydroxyethylphthalimide (192 mg) was suspended in ethanol (5 ml) and 2-hydroxyethyl-hydrazine (163 mg) was added and the reaction mixture was shaken over night at 1000 rpm. HPLC analysis of reaction mixture showed 70% conversion of starting after 18 hours.

Synthesis of N-(2-hydroxyethyl)-4-nitrophthalhydrazide

4-Nitrophthalimide (193 mg) was suspended in ethanol (5 ml) and 2-hydroxyethylhydrazine (163 mg) was added and the reaction mixture was shaken over night at 1400 rpm. HPLC analysis of reaction mixture showed 70% conversion of starting after 18 hours.

Synthesis of a solution-phase 5 phthalhydrazide-member library

A vial was loaded with phthalhydrazide (74 mg) and 4-nitrophthalimide (94 mg) and suspended in ethanol (3 ml). An ethanolic stock solution of hydrazine (1 eq.) and methylhydrazine (1 eq.) was added and the reaction mixture was shaken over night at 1000 rpm. HPLC analysis of reaction mixture showed conversion of starting after 16 hours. Products were isolated by

precipitation from addition of hexane (10 ml) and refrigeration. Centrifugation and washing with hexane (5 ml). Dried in vacuo. Library was dissolved in DMSO/H_2O (1/9, v/v) and was ready for analysis and or screening.

Synthesis of a solution-phase 33 phthalhydrazide-member library

5 different phthalimides (phthalimide, 4-nitrophthalimide, 3-nitrophthalimide, 4-chlorophthalimide and 4-fluorophthalimide) was reacted with 5 different hydrazines (hydrazine, methylhydrazine, N,N'-dimethylhydrazine, N,N'-diethylhydrazine and 2-hydroxyethylhydrazine) in a 6 x 6 matrix format yielding 25 individual compounds (plus 8 isomers), 10 indexed sub-libraries and 1 full library containing a mixture of all 33 different compounds. The reactions were carried out on the 1 mmole scale in the following way (as exemplified for phthalimide). Phthalimide (1 mmole) was placed in each of six 16 mm screw-capped reaction vials and dissolved/suspended in ethanol (or methanol). One of each of the different hydrazines (1 mmole) was added to vial 1 through 5. To vial 6 was added an equimolar mixture (i.e. 0.2 mmole) of each of the five different hydrazines to yield a sub-library. The base (N,N-diisopropylethylamine, 2-3 mmole) was added and reaction mixtures were fitted into an IKA-Vibrax-VXR shaker equipped with an Janke & Kunkel VX2 6 x 6-rack and was shaken for 1000-1400 rpm. In all cases with the 25 individual compounds we obtained a high yield of the expected phthalhydrazides including 8 isomers (HPLC analysis). Likewise, using reversed-phase HPLC (RP-HPLC), we were able to resolve all individual compounds in the indexed libraries. The resulting compounds could be isolated either by evaporation of solvent and base or by precipitation with hexane (10 ml), cooling and centrifugation.

Phthalimide functionalisation of chloromethylated polystyrene resin(Merrifield resin)

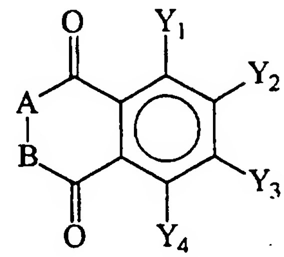
A chloromethylated polystyrene resin (930 mg, 0.88 mmole; Merrifield Peptide Resin, 1% cross-linked, loading 0.95 mmol eq./g) was suspended in N,N-dimethylformamide (12 ml) and stirred for 15 minutes at 100°C. Potassium phthalimide (310 mg, 1.67 mmol) was added and the reaction mixture stirred over night at 100°C. After cooling to room temperature, the resin was isolated by filtration and washed with N,N-dimethylformamide, dichloromethane and methanol. Dried in a vacuum dissicator. Yield 1.026 g.

4-Nitrophthalimide functionalisation of chloromethylated polystyrene resin (Merrifield resin)

A chloromethylated polystyrene resin (920 mg, 0.87 mmole; Merrifield Peptide Resin, 1% cross-linked, loading 0.95 mmol eq./g) was suspended in N,N-dimethylformamide (12 ml) and stirred for 15 minutes at 100°C. Potassium 4-nitrophthalimide (370 mg, 1.6 mmol) was added and the reaction mixture stirred for 24 hours at 100°C. After cooling to room temperature, the resin was isolated by filtration and washed with N,N-dimethylformamide, dichloromethane and methanol. Dried in a vacuum dissicator. Yield 1.102 g.

CLAIMS

1. A method for producing a combinatorial library, {D}={P}, of compounds of the general formula I



I

wherein each of A and B independently is selected from the group consisting of -N(R^1)-, -O-, -S-, -Se-, and -Te-,

wherein each R^1 independently designates hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted C_{2-20}-alkynyl, optionally substituted aryl, optionally substituted heteroaryl, and

each of Y_1, Y_2, Y_3, and Y_4 independently designates hydrogen; optionally substituted C_{1-20}-alkyl; optionally substituted C_{2-20}-alkenyl; optionally substituted C_{4-20}-alkadienyl; optionally substituted C_{6-20}-alkatrienyl; optionally substituted C_{2-20}-alkynyl; hydroxy; optionally substituted aryl; optionally substituted aryl-C_{1-6}-alkyl; optionally substituted aryloxy-C_{1-6}-alkyl; optionally substituted heteroaryl; optionally substituted heteroaryl-C_{1-6}-alkyl; optionally substituted heteroaryloxy-C_{1-6}-alkyl; halogen such as fluoro, chloro, bromo, and iodo; cyano; nitro; O-R^2; formyl, carboxy, -CO-O-R^2, -CO-R^2, -O-CO-R^2; amino; -N(R^2)H; mono- or di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl; -N(R^2)R^3; -N(R^3)-CO-R^2; (C_{1-20}-alkyl)carbonylamino-C_{1-6}-alkyl; carbamoyl, aminocarbonyl-C_{1-6}-alkyl; mono- or di-(C_{1-20}-alkyl)aminocarbonyl; mono- or di(C_{1-6}-alkyl)aminocarbonyl-C_{1-6}-alkyl; sulphanyl; optionally substituted C_{1-20}-alkylthio-C_{1-6}-alkyl; optionally substituted alkylthio; (optionally substituted aryl)thio; guanidino; guanidino-C_{1-6}-alkyl; sulphono (-SO_3H); sulphino (-SO_2H); halosulphonyl; -S(O)$_m$-N(R^2)$_2$ where m is 2 or 3; -S(O)$_m$-NH(R^2) where m is 2 or 3; -S(O)$_m$-NH_2 where m is 2 or 3; isocyano; isothiocyano; thiocyano; -OP(O)$_p$(R^2)$_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; and -N(R^3)P(O)$_p$(R^2)$_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5;

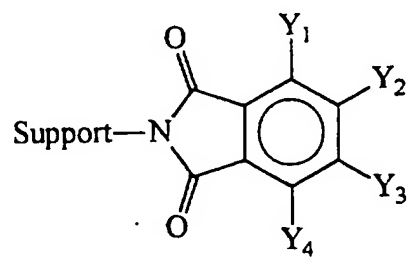
wherein each R^2 independently designates a group selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted C_{2-20}-alkynyl, optionally substituted aryl, optionally substituted heteroaryl; and R^3 independently designates a group selected from hydrogen and C_{1-6}-alkyl;

or one or two of the substituent pairs, Y_1/Y_2, Y_2/Y_3, Y_3/Y_4, may each form a biradical which, together with the atoms located between the substituents in question, form(s) either a 4-, 5-, 6-, 7- or 8-membered ring, where the biradical is a 2-, 3-, 4-, 5-, or 6-membered partially or fully

saturated carbon chain optionally interrupted and/or terminated by one or more heteroatoms selected from nitrogen, oxygen, and sulphur, and where the biradical may be substituted with one, two, three, or several substituents as defined for Y^1-Y^4;

comprising

(a) providing an array {P} of at least two different support-immobilised phthalimido moiety species of the general formula II



II

wherein "Support" indicates a polymeric support unit to which the phthalimido moiety species are covalently bound, and Y_1, Y_2, Y_3, and Y_4 are as defined above,

and (b) cleaving the support-immobilised phthalimido moiety species, or a least a part thereof, from the support units to which they are immobilised by reacting the support units with an array {D} of at least one, preferably at least two, dinucleophile species of the general formula A'-B' (corresponding to A-B in formula I), wherein each of A' and B' independently is selected from the group consisting of -N(R^1)H, -OH, -SH, -SeH, -TeH, wherein each R^1 is as defined above; whereby the 5-membered ring of the phthalimido moiety (formula II) is converted to a 6-membered ring (formula I), the identity of which is dependent of the identity of the dinucleophile (A'-B') with which the moiety species has been reacted.

2. A method according to claim 1, wherein one of A and B is -N(R^1)- and the other is selected from the group consisting of -N(R^1)-, -O-, -S-, -Se-, and -Te-, wherein each R^1 independently designates hydrogen, optionally substituted $C_{1\text{-}20}$-alkyl, optionally substituted $C_{2\text{-}20}$-alkenyl, optionally substituted $C_{4\text{-}20}$-alkadienyl, optionally substituted $C_{6\text{-}20}$-alkatrienyl, optionally substituted $C_{2\text{-}20}$-alkynyl, optionally substituted aryl, optionally substituted heteroaryl; and wherein A' and B' corresponds to A and B in formula I.

3. A method according to claim 2, wherein one of A and B is -N(R^1)- and the other is selected from the group consisting of -N(R^1)- and -O-, preferably -N(R^1)- wherein each R^1 independently designates hydrogen, optionally substituted $C_{1\text{-}20}$-alkyl, optionally substituted $C_{2\text{-}20}$-alkenyl, optionally substituted $C_{4\text{-}20}$-alkadienyl, optionally substituted $C_{6\text{-}20}$-alkatrienyl, optionally substituted $C_{2\text{-}20}$-alkynyl, optionally substituted aryl, optionally substituted heteroaryl.

4. A method according to any of the claims 1-3, wherein R^1 designates hydrogen, C_{1-6}-alkyl, optionally substituted aryl, optionally substituted heteroaryl.

5. A method according to any of the preceding claims, wherein each of Y_1, Y_2, Y_3, and Y_4 independently designates hydrogen; optionally substituted C_{1-6}-alkyl; hydroxy, optionally substituted aryl; optionally substituted aryl-C_{1-6}-alkyl; optionally substituted aryloxy-C_{1-6}-alkyl; optionally substituted heteroaryl; optionally substituted heteroaryl-C_{1-6}-alkyl; optionally substituted heteroaryloxy-C_{1-6}-alkyl; halogen; cyano; nitro; O-R^2; formyl, carboxy, -CO-O-R^2, -CO-R^2, -O-CO-R^2; amino; -N(R^2)H; mono- or di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl; -N(R^2)R^3; -N(R^3)-CO-R^2; (C_{1-20}-alkyl)carbonylamino-C_{1-6}-alkyl; carbamoyl, aminocarbonyl-C_{1-6}-alkyl; mono- or di-(C_{1-6}-alkyl)aminocarbonyl; mono- or di(C_{1-6}-alkyl)aminocarbonyl-C_{1-6}-alkyl; sulphanyl; sulphono (-SO_3H); sulphino (-SO_2H); halosulphonyl; -$S(O)_m$-$N(R^2)_2$ where m is 2 or 3; -$S(O)_m$-$NH(R^2)$ where m is 2 or 3, -$S(O)_m$-NH_2 where m is 2 or 3; isocyano; isothiocyano; thiocyano; -$OP(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; and -$N(R^3)P(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5;

wherein each R^2 independently designates a group selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted aryl, optionally substituted heteroaryl; and R^3 independently designates a group selected from hydrogen and C_{1-6}-alkyl;

or one or two of the substituent pairs, Y_1/Y_2, Y_2/Y_3, Y_3/Y_4, may each form a biradical which, together with the atoms located between the substituents in question, form(s) either a 4-, 5-, 6-, 7- or 8-membered ring, where the biradical is a 2-, 3-, 4-, 5-, or 6-membered partially or fully saturated carbon chain optionally interrupted and/or terminated by one or more heteroatoms selected from with from nitrogen, oxygen, and sulphur, and where the biradical may be substituted with one, two, three, or several substituents as defined for Y^1-Y^4.

6. A method according to claim 5, wherein each of Y_1, Y_2, Y_3, and Y_4 independently designates hydrogen; optionally substituted C_{1-6}-alkyl; hydroxy, optionally substituted aryl; optionally substituted aryl-C_{1-6}-alkyl; optionally substituted aryloxy-C_{1-6}-alkyl; optionally substituted heteroaryl; optionally substituted heteroaryl-C_{1-6}-alkyl; optionally substituted heteroaryloxy-C_{1-6}-alkyl; halogen; cyano; nitro; O-R^2; formyl, carboxy, -CO-O-R^2, -CO-R^2, -O-CO-R^2; amino; -N(R^2)H; mono- or di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl -N(R^2)R^3; -N(R^3)-CO-R^2; (C_{1-20}-alkyl)carbonylamino-C_{1-6}-alkyl; carbamoyl, aminocarbonyl-C_{1-6}-alkyl; mono- or di-(C_{1-20}-alkyl)aminocarbonyl; mono- or di(C_{1-6}-alkyl)aminocarbonyl-C_{1-6}-alkyl; sulphanyl; sulphono (-SO_3H); sulphino (-SO_2H);

wherein each R^2 independently designates a group selected from hydrogen, optionally substituted C_{1-6}-alkyl, optionally substituted heteroaryl; and R^3 independently designates a group selected from hydrogen and C_{1-6}-alkyl.

7. A method according to claim 5 or 6, wherein in one of the substituent pairs, Y_1/Y_2, Y_2/Y_3, Y_3/Y_4, may each form a biradical which, together with the atoms located between the substituents in question, form(s) either a 4-, 5-, 6-, 7- or 8-membered ring, where the biradical is a 2-, 3-, 4-, 5-, or 6-membered partially or fully saturated carbon chain optionally interrupted and/or terminated by one or more heteroatoms selected from with from nitrogen, oxygen, and sulphur, and where the biradical may be substituted with one, two, three, or several substituents as defined for Y^1-Y^4.

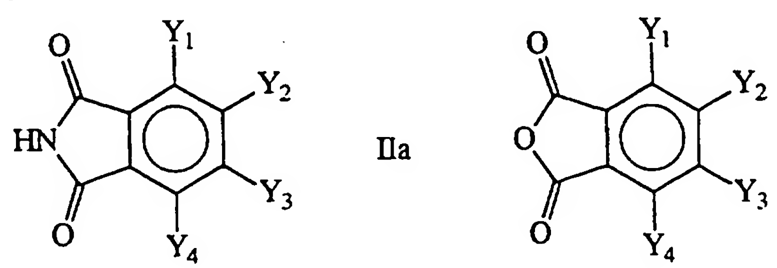
8. A method according to any of the preceding claims, wherein, when any of the substituent pairs Y_1/Y_2, Y_2/Y_3, and Y_3/Y_4 form(s) a biradical, this biradical, together with the atoms located between the substituents in question, represents a ring fused to the bicyclic ring system represented by the formula I, the ring being selected from benzene, furane, 2,3-dihydrofuran, 2,5-dihydrofuran, isoxazole, oxazole, thiazole, isothiazole, imidazole, triazole, cyclobutene, pyroline, pyrrole, cyclopentene, cyclopentadiene, cyclohexene, and cyclohexadiene.

9. A method according to any of the preceding claims, wherein the array {P} consists of at least three, preferably four, such as five, different support-immobilised phthalimido moiety species.

10. A method according to any of the preceding claims, wherein the array {D} consists of at least two, preferably three, such as four, different dinucleophile species.

11. A method according to any of the preceding claims, wherein the combinatorial library {D}={P} comprises at least 10, such as between 10 and 100, different species of the formula I.

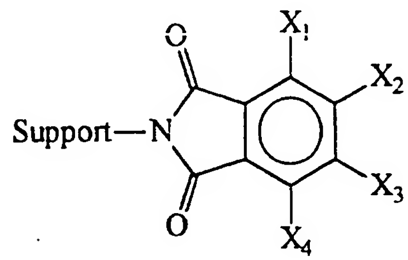
12. A method according to any of the preceding claims, wherein the array {P} of support-immobilised phthalimido moiety species of the general formula II is provided by immobilising an array $\{P_{ab}\}$ of phthalimido moieties of the general formula IIa or IIb



IIa IIb

wherein Y_1, Y_2, Y_3, and Y_4 designate the same groups as defined for the support-immobilised phthalimido moieties of the formula II constituting the array {P} of support-immobilised phthalimido moieties of the general formula II, to a solid support material.

13. A method according to any of the claims 1-11, comprising attaching phthalimido moieties to units of a support to obtain an array {P} of support-immobilised phthalimido moiety species of the general formula III

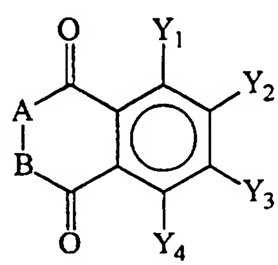


III

in which "Support" indicates a polymeric support to which the phthalimido moieties are covalently bound, and each of X_1, X_2, X_3, and X_4 independently designate substituents or biradicals as defined for Y_1, Y_2, Y_3, and Y_4; and

performing one or several chemical reactions by contacting the support units carrying the immobilised phthalimido moieties, either together or divided into subgroups of units, with one or several reagents, the contacting in the case of several reagents being performed simultaneously or sequentially, or by using combinations of simultaneous contacting and sequential contacting; whereby an array of support-immobilised phthalimido moiety species of the general formula II is provided.

14. A composition comprising at least two different compounds of the general formula I



I

wherein each of A and B independently is selected from the group consisting of -N(R^1)-, -O-, -S-, -Se-, and -Te-,

wherein each R^1 independently designates hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted C_{2-20}-alkynyl, optionally substituted aryl, optionally substituted heteroaryl, and

each of Y_1, Y_2, Y_3, and Y_4 independently designates hydrogen; optionally substituted C_{1-20}-alkyl; optionally substituted C_{2-20}-alkenyl; optionally substituted C_{4-20}-alkadienyl; optionally substituted C_{6-20}-alkatrienyl; optionally substituted C_{2-20}-alkynyl; hydroxy; optionally substituted aryl; optionally substituted aryl-C_{1-6}-alkyl; optionally substituted aryloxy-C_{1-6}-alkyl; optionally substituted heteroaryl; optionally substituted heteroaryl-C_{1-6}-alkyl; optionally substituted heteroaryloxy-C_{1-6}-alkyl; halogen such as fluoro, chloro, bromo, and iodo; cyano; nitro; O-R^2;

formyl, carboxy, -CO-O-R^2, -CO-R^2, -O-CO-R^2; amino; -N(R^2)H; mono- or di(C_{1-6}-alkyl)amino-C_{1-6}-alkyl; -N(R^2)R^3; -N(R^3)-CO-R^2; (C_{1-20}-alkyl)carbonylamino-C_{1-6}-alkyl; carbamoyl, aminocarbonyl-C_{1-6}-alkyl; mono- or di-(C_{1-20}-alkyl)aminocarbonyl; mono- or di(C_{1-6}-alkyl)aminocarbonyl-C_{1-6}-alkyl; sulphanyl; optionally substituted C_{1-20}-alkylthio-C_{1-6}-alkyl; optionally substituted alkylthio; (optionally substituted aryl)thio; guanidino; guanidino-C_{1-6}-alkyl; sulphono (-SO_3H); sulphino (-SO_2H); halosulphonyl; -$S(O)_m$-$N(R^2)_2$ where m is 2 or 3; -$S(O)_m$-$NH(R^2)$ where m is 2 or 3; -$S(O)_m$-NH_2 where m is 2 or 3; isocyano; isothiocyano; thiocyano; -$OP(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5; and -$N(R^3)P(O)_p(R^2)_q$ where p is 1, 2, or 3, q is 1 or 2, and p+q is 3, 4, or 5;

wherein each R^2 independently designates a group selected from hydrogen, optionally substituted C_{1-20}-alkyl, optionally substituted C_{2-20}-alkenyl, optionally substituted C_{4-20}-alkadienyl, optionally substituted C_{6-20}-alkatrienyl, optionally substituted C_{2-20}-alkynyl, optionally substituted aryl, optionally substituted heteroaryl; and R^3 independently designates a group selected from hydrogen and C_{1-6}-alkyl;

or one or two of the substituent pairs, Y_1/Y_2, Y_2/Y_3, Y_3/Y_4, may each form a biradical which, together with the atoms located between the substituents in question, form(s) either a 4-, 5-, 6-, 7- or 8-membered ring, where the biradical is a 2-, 3-, 4-, 5-, or 6-membered partially or fully saturated carbon chain optionally interrupted and/or terminated by one or more heteroatoms selected from nitrogen, oxygen, and sulphur, and where the biradical may be substituted with one, two, three, or several substituents as defined for Y^1-Y^4

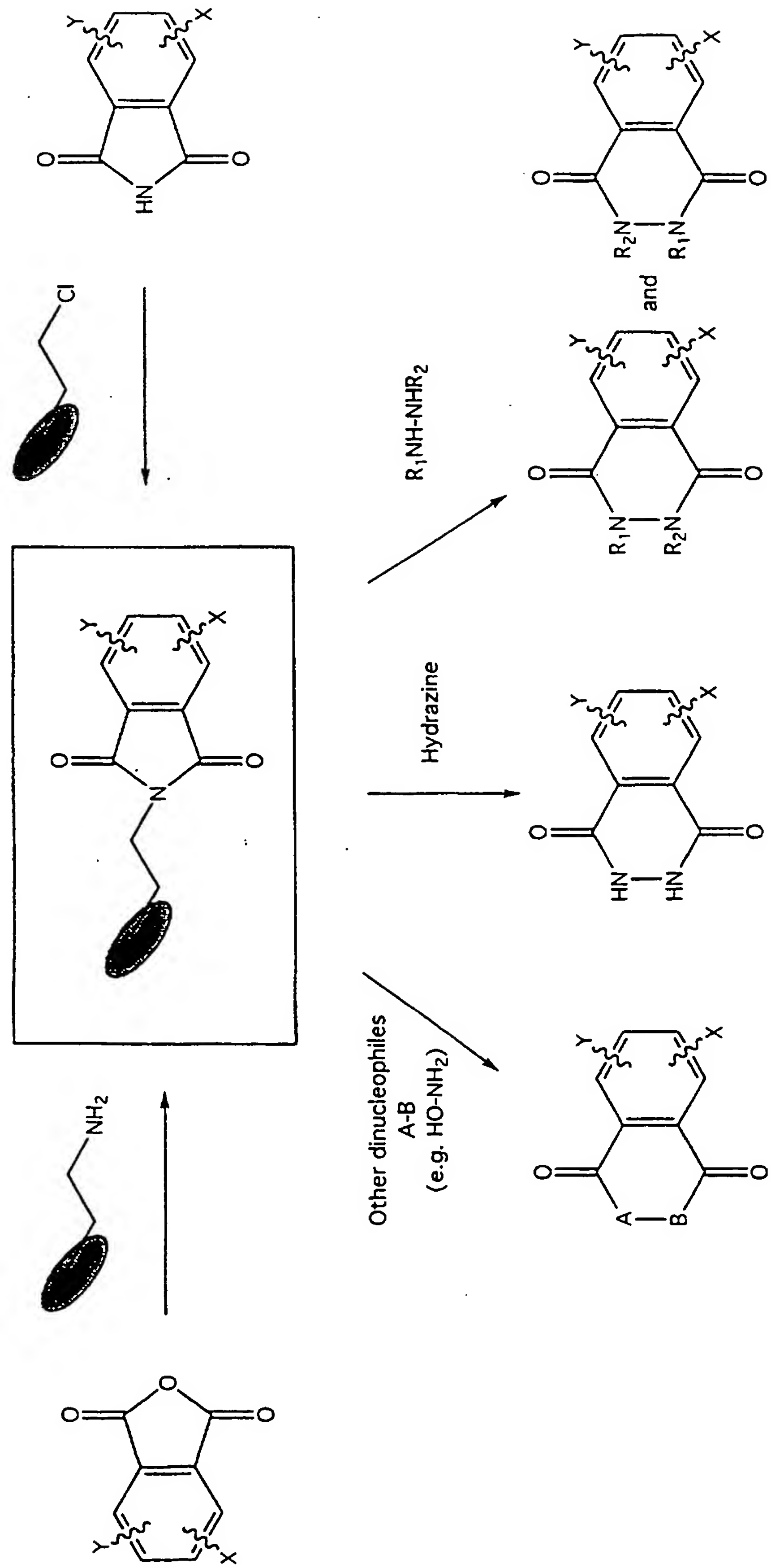
15. A composition according to claim 14, comprising at least four, preferably at least six, in particular at least ten, such as between 10 and 100, different compounds of the general formula I.

16. A composition according to claim 14 or 15, which comprises a solvent wherein the compounds, or salts or acid addition salts thereof, are dissolved.

17. A composition according to any of the claims 14-16, which, except for any solvents, is substantially free of compounds not being of the formula I.

18. A composition according to any of the claims 14-17, which is obtainable by the method defined in any of the claims 1-13.

19. A composition according to any of the claims 14-17, which is obtained by the method defined in any of the claims 1-13.



Cl
NH2
R1NH-NHR2
and
Hydrazine
Other dinucleophiles
A-B
(e.g. HO-NH2)

Fig. 1

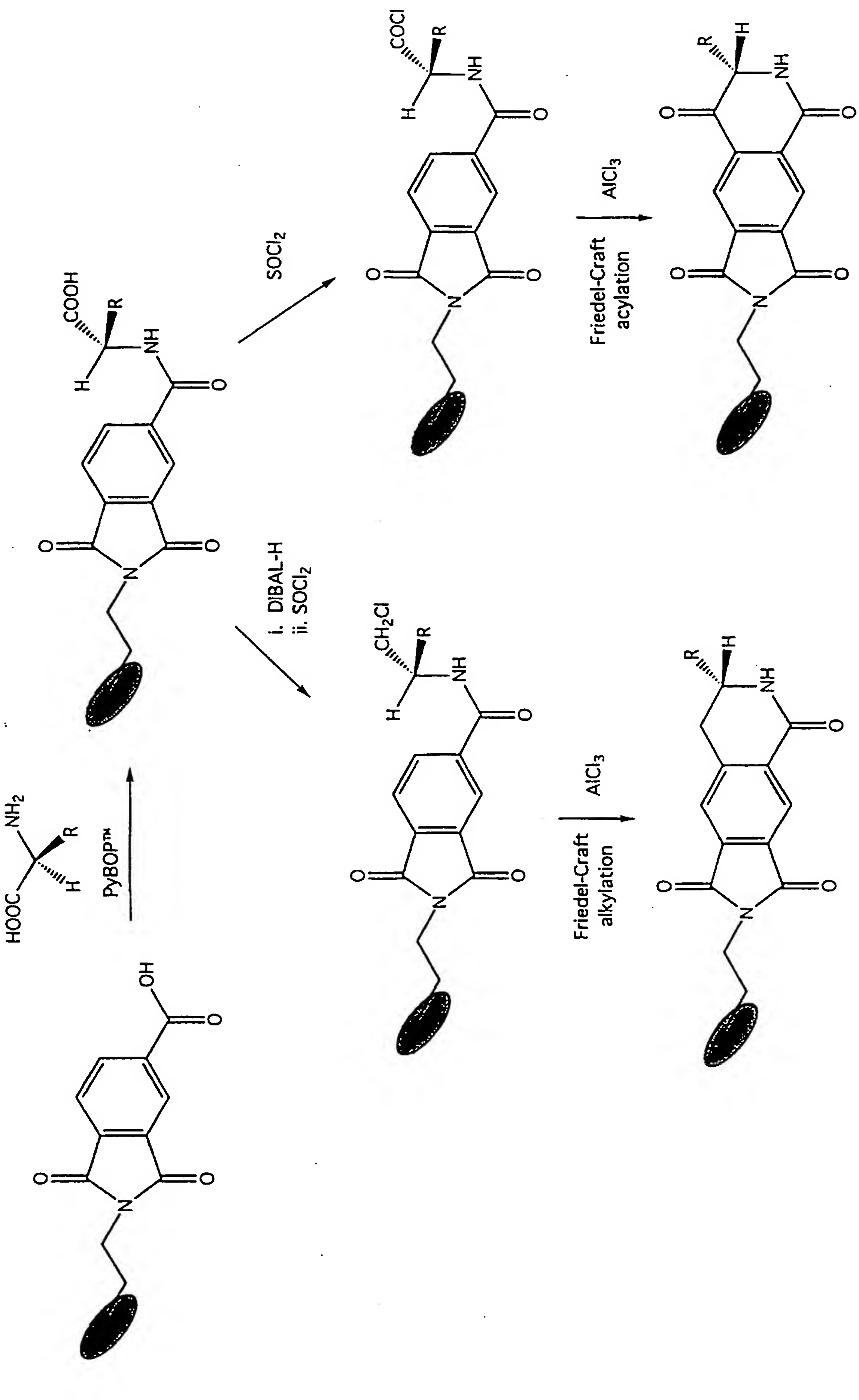

HOOC
NH2
R
H
PyBOP™
OH
COOH
NH
SOCl2
i. DIBAL-H
ii. SOCl2
COCl
CH2Cl
AlCl3
Friedel-Craft
acylation
Friedel-Craft
alkylation

Fig. 2

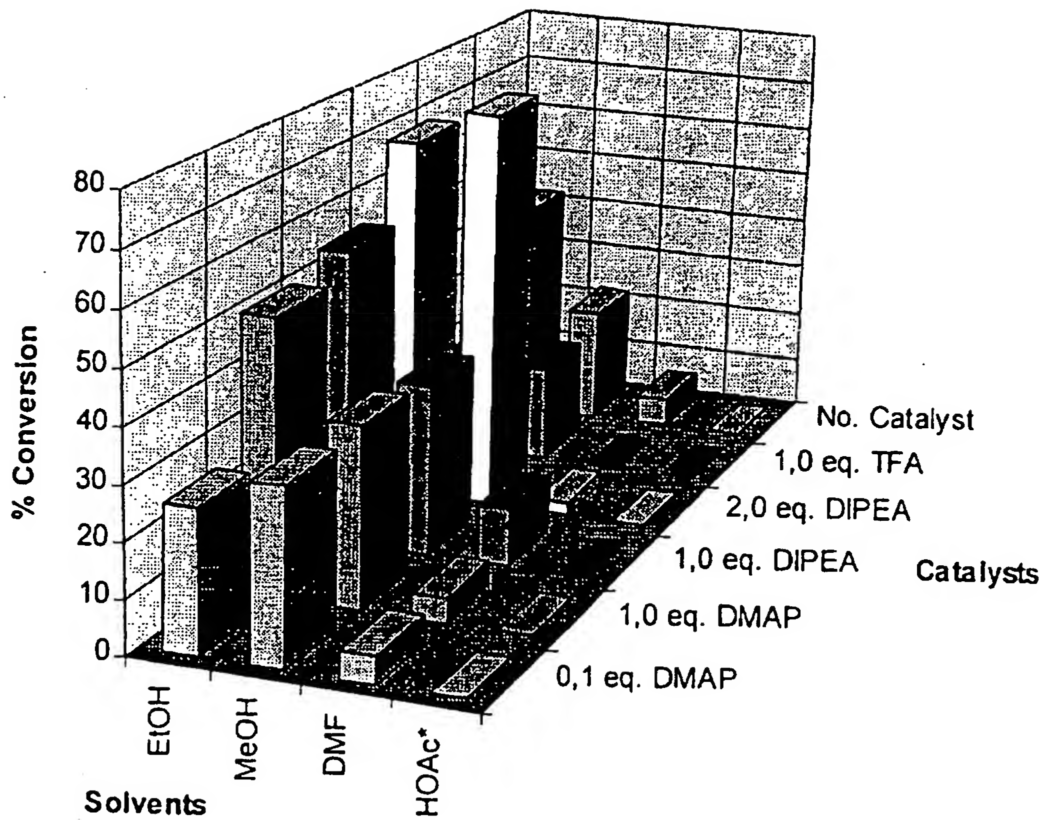

80
70
60
50
40
30
20
10
0
% Conversion
No. Catalyst
1,0 eq. TFA
2,0 eq. DIPEA
1,0 eq. DIPEA
1,0 eq. DMAP
0,1 eq. DMAP
Catalysts
EtOH
MeOH
DMF
HOAc*
Solvents

Fig. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00534

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 237/32
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS-ONLINE, WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	Tetrahedron Letters, Volume 37, No 19, 1996, John Nielsen et al, "Implementation of a Combinatorial Cleavage and Deprotection Scheme. 1. Sunthesis of Phthalhydrazide Libraries" page 3351 - page 3354 --	1-19
A	FR 2433517 A (MILES LABORATORIES, INC.), 14 March 1980 (14.03.80), page 9, line 4 - line 8 -- --------	1-19

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" erlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 March 1997	19-03-1997

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 96/00534

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
FR-A- 2433517	14/03/80	CA-A- 1137975	21/12/82
		CA-A- 1147336	31/05/83
		CA-A- 1147737	07/06/83
		DE-A,C- 2928048	07/02/80
		GB-A,B- 2026159	30/01/80
		GB-A,B- 2041920	17/09/80
		GB-A,B- 2041921	17/09/80
		JP-A- 55018996	09/02/80
		US-A- 4212805	15/07/80
		US-A- 4226993	07/10/80
		US-A- 4297273	27/10/81
		US-A- 4334069	08/06/82